CLT CONFERENCES
The 2006 Biotechnology Law Update

How to get Medicinal Products through the Regulatory Process

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INTRODUCTION

- Licensing of Pharmaceutical Products
- Licensing Structures for Bioinformatics Products
- Advertising, Marketing and Promotion of Medicinal Products in compliance with UK and EU Legislations and various Industry Codes
- Post-marketing obligations such as Pharmacovigilance

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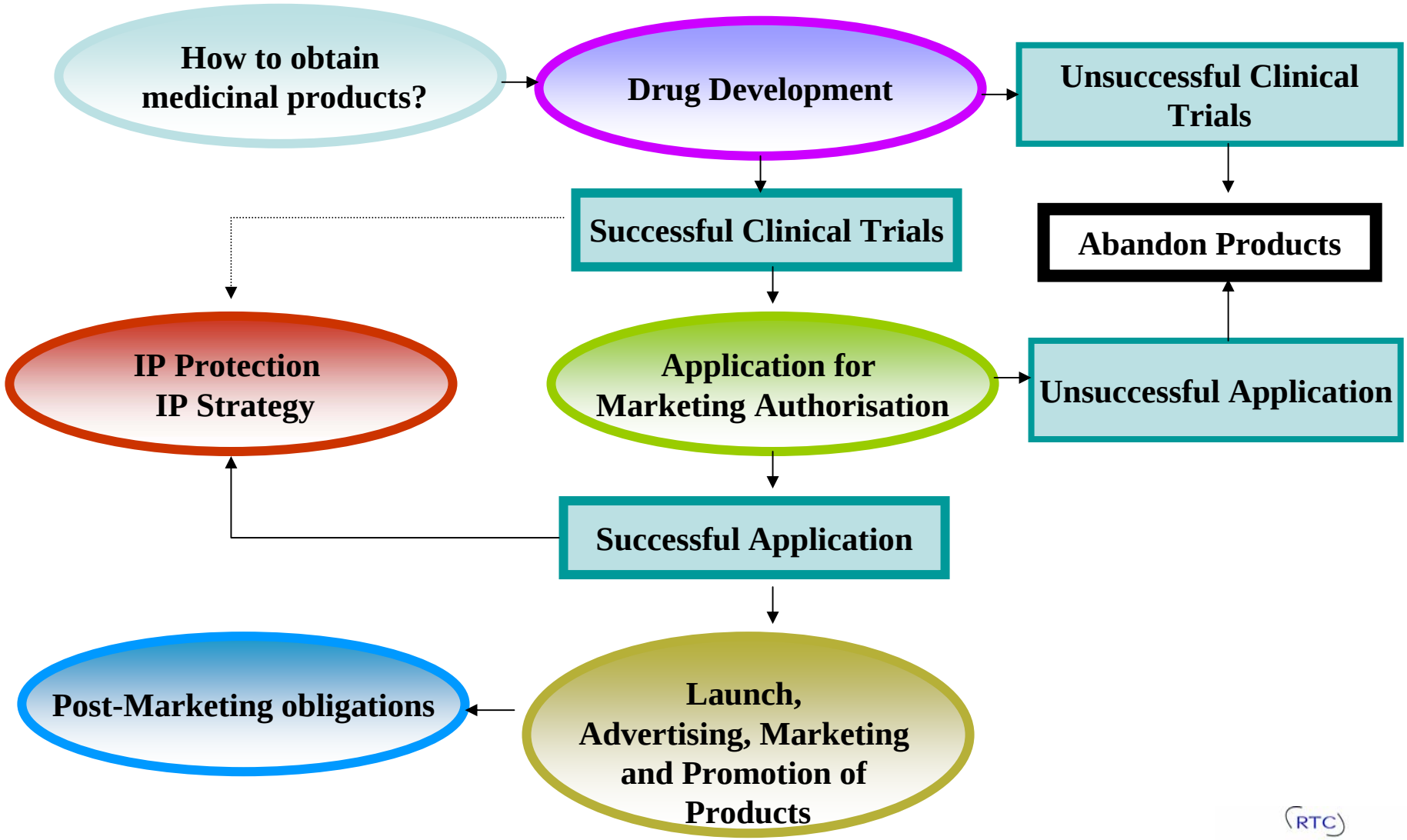
KEY STEPS



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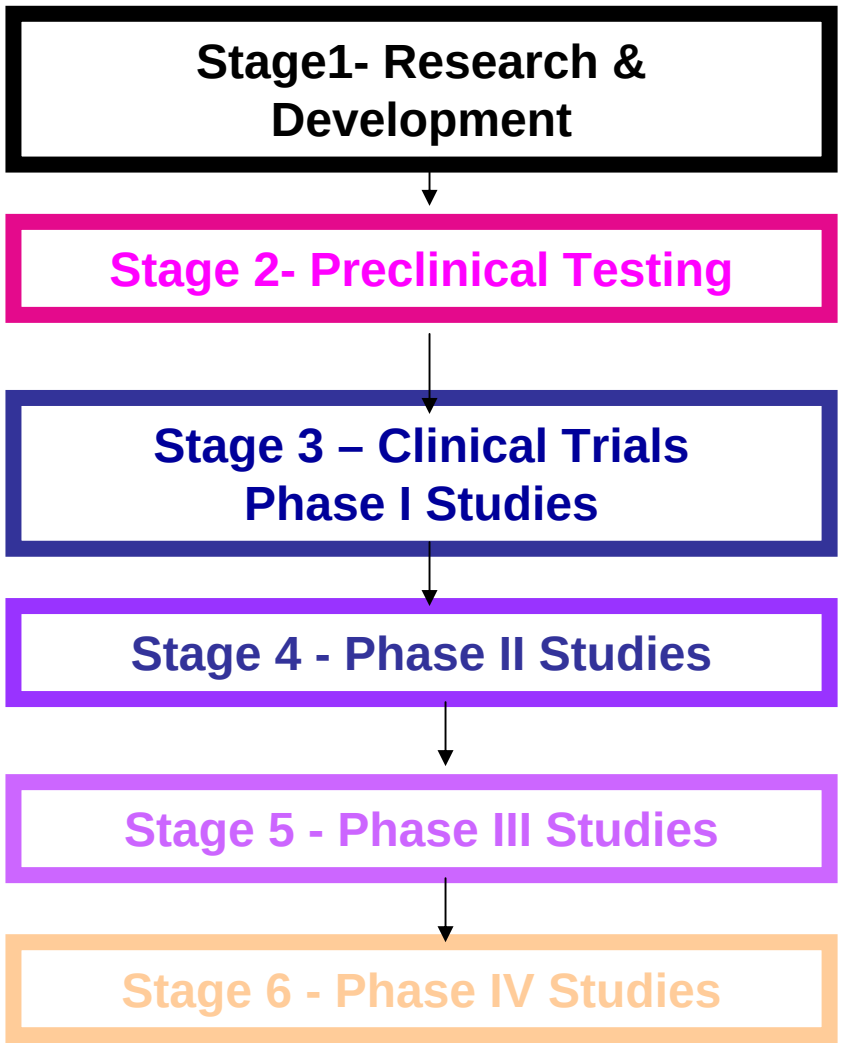
Drug Development

STAGES OF DRUG DEVELOPMENT



Medicinal and Pharmaceutical Products

Licensing Medicinal Products Overview

- **Definition of a Medicinal Product**

Directive 2001/83/EEC (as amended) defines a "medicinal product" as:

"(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

e.g. pharmaceutical products

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Licensing Medicinal Products Overview

➢ What are not Medicinal Products?

- Products which claim to “maintain” or “help to maintain” or “support” health or a healthy lifestyle, are not considered medicinal in themselves

- Unless “health maintenance” claims suggest or imply that the product may restore, or help to restore, a specific bodily function or organ to a normal healthy state

Licensing Medicinal Products Overview

➢ What are Pharmaceutical Products?

- ‘Pharmaceutical Products are defined as any products of the pharmaceutical sector, including medicinal products under Directive 200/83/EC

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Application for Marketing Authorisation

Licensing Medicinal Products Overview

- A medicinal product may not generally be placed on the market without a **marketing authorisation**.

- A parallel system operates in relation to the grant of marketing authorisations.

- European Union Centralised System
  - single authorisation valid throughout the European Union is issued by the **European Commission (the system operating under EC Council Regulation 2309/93**)

- UK System - authorisations issued by MHRA **(Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994, SI 1994/3144).**

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Licensing Medicinal Products Overview

- **Marketing Authorisations – EU and UK**
  - **EU - European Medicines Evaluation Agency (EMEA)** http://www.emea.eu.int/
  - **UK - The Medicines and Healthcare Products Regulatory Agency (MHRA)** http://www.mhra.gov.uk

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Licensing Medicinal Products Overview - EMEA

➢ Centralised System

- Obligatory for biotechnology products
- Compulsory for new products for treatment of AIDS, cancer, neurodegenerative diseases and diabetes
- Medicinal Products via this route have longer period of exclusivity (10 years) compared to decentralised system (8 years)

➢ Decentralised System

- Under this system the CPMP co-ordinates procedure, but does not take part in the decision-making process unless disagreement between member states

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Licensing Medicinal Products Overview - EMEA

➢ Centralised System

- **Application**
- – file an application with the EMEA
- – application passed to Committee for Proprietary Medicinal Products (CPMP)
- – representatives from two member states selected to consider application, one chosen by the pharmaceutical company i.e. the "rapporteur" and "co-rapporteur" member states

➢ Decentralised System

- **Application**
- – Following receipt of application, CPMP contracts one member state to assess application
- – The contracted state is called the reference member state (RMS)
- – In the UK RMS is the MHRA
- – The RMS is contracted to grant a licence within a maximum of 210 days.

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Licensing Medicinal Products Overview - EMEA

➢ Centralised System

- **Application**

– assessment of application by CPMP

– CPMP gives "opinion" on application- considered by the EU Commission

– CPMP works to strict timetable laid down in EU law

– An "opinion" has to be issued within 210 days of receipt of the application, although the company may stop the procedure at any time

➢ Decentralised System

- **Application**

– Company applying for licence has right to choose RMS

– once RMS approves product member states have 90 days to '**mutually recognise**' approval

– If countries raise objections about safety, major scientific or public health issues - CPMP acts as arbitrator and has 30 days to make decision

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Licensing Medicinal Products Overview - EMEA

- **Centralised System**
  - **Application**
  - preliminary review undertaken early in process
  - result revealed to company - decide to continue or withdraw application
  - under new proposals advice given to companies prior to application should improve to tackle problem of premature applications and withdrawals

- **Decentralised System**
  - **Application**
  - the advice of CPMP to EU Commission is binding
  - each country issues own marketing authorisation
  - Once a product has a marketing authorisation product ‘licensed’,registered’ or ‘approved’

Licensing Medicinal Products Overview - EMEA

- **Centralised System**
  - **Application**
  - Summaries of CPMP opinion published on EMEA's website
  - Average time = 180 days
  - If opinion is **negative** company must answer questions raised by CPMP before the application can be progressed
  - If opinion is **positive**, the EU Commission requests comments from other member states - 28 days to respond.
  - Any objections to rapporteur's decision considered by CPMP - makes recommendation for or against an EU-wide licence
  - If licence is recommended a European Public Assessment Report (EPAR) is produced and **marketing authorisation issued**
  - Company is **able to market** in any EU country- may decide not to launch in a particular country for commercial reasons or due to suitability of market

Licensing Medicinal Products Overview – Launch Cont'd

- **Other factors**
  - Pricing negotiations - can significantly delay launch
  - UK – median time from marketing authorisation to launch 20 days
  - Decentralised route - different outcomes in different countries
  - Pharmaceutical companies prefer mutual recognition route - offers greater chance of approval
  - UK system one of the fastest then Swedish system
  - Under the new proposals likely that licences will be reviewed after five years and licence renewal will be done on the basis of a comparative reassessment of the product's risk benefit balance

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Licensing Medicinal Products Overview - MHRA

- **Via MHRA**
  - Regulatory authority for medicines in the UK
  - A substantial part of the MHRA's work is to support the European process
  - However, whether the MHRA receives an application for a product licence as the sole agency or as part of the European system, the processes involved are essentially the same
  - New or abridged Application

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Licensing Medicinal Products Overview - MHRA

➢ Via MHRA

- **Application**

  – Pharmaceutical company submits file to MHRA or via EMEA

  – Submitted applications must provide **sufficient evidence** of **adequate quality for intended use** and **sufficiently safe and effective**

  – The application **dossier** consists of:-
    - Administrative data
    - Packaging
    - Samples
    - Manufacturing and marketing authorisations applied for or obtained elsewhere
    - Summary of product characteristics
    - Patient package leaflet
    - Expert reports

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Licensing Medicinal Products Overview - MHRA

- **Via MHRA**
  - **Application**
    - For **new** applications i.e. for products containing **new active substances**, toxicological, pharmacological and clinical data must be provided along with a fee of **£80,698.00**
    - Applications are available from MHRA website

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Licensing Medicinal Products Overview - MHRA

➢ Via MHRA

- **Application**
  - Application reviewed and assessed by Committee on Safety of Medicines (CSM)
  - The CSM is the advisory committee in the UK that can be considered equivalent to the CPMP in the EU
  - The CSM will either recommend licence be granted, accept application subject to modifications or reject application with reasons
  - If CSM recommends granting a licence – if licensing authority believes medicine is of **acceptable quality**, is **safe** and **effective** and **can give overall benefit to patients**, a **licence granted**.

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Licensing Medicinal Products Overview - MHRA

➢ Via MHRA

- **Application**

  – If no additional information requested the time from application to the granting of licence = 70 working days

  – If application rejected, company can appeal to the Medicines Commission - an advisory body established under the Medicines Act

  – Medicines Commission - comprises a group of experts, appointed by health ministers, who reassess the data and advise the Licensing Authority

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New Developments

New Developments

➢ Compulsory Licensing

- Proposed Regulation on Compulsory Licensing for the export of generic medicines to Developing Countries

- On 1 December 2005, European Parliament adopted at first reading the Commission's Proposal of 29 October 2004 on a regulation on compulsory licensing for the **export of generic medicines** to **developing countries**

- The regulation allows companies to produce generic copies of patented medicines in order to export them to developing countries that have no, or hardly any, manufacturing capability

New Developments

➢ Compulsory Licensing

- The regulation will implement new obligation of EU under the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), as amended by a decision of the WTO General Council decision of 6 December 2005

- Prior to this amendment, TRIPS only enabled countries with major public health concerns to issue compulsory licences for the manufacture of patent protected medicines in their own territory; few developing countries, however, have a pharmaceutical industry capable of producing the generic drugs

- The new amendment introduces possibility of exporting generic drugs from manufacturing countries into developing countries that lack pharmaceutical manufacturing capability, even where these drugs are patent-protected in the manufacturing country

New Developments

➢ Compulsory Licensing

- Applications must be submitted to competent authority in member states where patents or supplementary protection certificates have effect and cover intended activities of manufacture and sale for export (Article 5(1))

- The applicant needs:-
  - evidence of specific request from an authorised representative of importing country or from a non-governmental organisation, UN body or other international health organisation acting with the formal authorisation of that importing country (Article 5(3)(g))

  - to demonstrate that it was not successful in obtaining an authorisation from the rights holder (Article 7(1))

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Export Certificates

Export Certificates

➢ Export Certificates

- MHRA issues export certificates on request to assist exporters of medicinal products to satisfy the import requirements of other countries
- Certificates issued by MHRA indicate whether product or manufacturer to which the certificate applies has met statutory requirements
- Format of certificates usually complies with that specified by international authorities e.g. World Health Organisation (WHO) and MHRA will not deviate from the agreed format
- MHRA issues four different types of export certificates, two of which comply with the format established by the WHO and reflect UK participation in the WHO scheme
- Each type of certificate is country specific, naming one individual country - the EU is not acceptable as a one-country unit
- The fee is same for each type of certificate but varies dependant on turnaround
- *Costs* - £53 or £118 (urgent).

Advertising Marketing and Promotions

Advertising, Marketing and Promotion of Medicines

➢ Regulation of what types of Advertising?

- "**Advertisement**" has a broad definition under the Advertising Regulations (its meaning is assigned by Regulation 2(2) of the Advertising Regulations by reference to section 92 of the Medicines Act 1968)
  - encompasses written and spoken words highlighting qualities of the medicines ("product claims") intended to encourage prescription or supply by health professionals and use of medicines by the general public
  - excluded - reference material, factual informative statements or announcements, trade catalogues and price lists, provided that they do not make a product claim

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Advertising, Marketing and Promotion of Medicines

➢ Advertising Applied to Medicines

- The definition of **Advertising applied to medicines** includes-

  - articles in published journals
  - magazines and newspapers
  - posters and notices
  - photographs
  - film
  - broadcast material
  - video recording, electronic transmissions and material posted on the Internet
  - point-of-sale materials, leaflets, booklets and other promotional materials that include specific product claims and which are supplied separately from the product may also be considered advertisements
  - words from a soundtrack or video recording are within the definition of advertising as is the spoken word

Legislation that applies to Advertising and Promotion of Medicine

Legislation that applies to Advertising and Promotion of Medicines

➢ Relevant Legislations

- UK Legislations:-

  - **The Medicines (Advertising) Regulations 1994** ("the Advertising Regulations")

  - **The Medicines (Monitoring of Advertising) Regulations 1994** ("the Monitoring Regulations") as amended

- These implement Title VIII of **European Directive 2001/83/EC**

- The Advertising Regulations contain rules on the contents of advertisements and promotions

- The Monitoring Regulations contain provisions for enforcing the Advertising Regulations

Legislation that applies to Advertising and Promotion of Medicines

The Medicines (Advertising) Regulations 1994

- **Reg 6** - prohibits misleading adverts leading to use of relevant medicinal products for the purpose of the treatment, prevention or diagnosis of any disease specified in, or any disease falling within a class of disease specified in, Schedule 1 (e.g. bone disorders, genetic disorders)
- **Reg7** - prohibits misleading advertisements leading to supply of medicinal products for prescription only
- **Reg 9-** prohibits a wide range of advertisement e.g. advertisements which give the impression that a medical consultation or surgical operation is unnecessary or suggest that health can be enhanced by taking the medicinal product
- **Reg10**- sets out form and content required of advertisements of medicinal products to the public - advertisement must be clear that the message so product is clearly identified as a medicinal product, and:

  (i) the name of the medicinal product;

  (ii) if it contains only one active ingredient, the common name of the medicinal product,

  (iii) the information necessary for correct use of the medicinal product; and

  (iv) an express and legible invitation to read carefully the instructions on the leaflet contained within the package or on the label, as the case may be

Legislation that applies to Advertising and Promotion of Medicines

- Title VIII of the Codified Directive has been amended by **Directive 2004/27/EC**:-

  - this guidance removes prohibitions on advertising medicinal products for certain diseases and on mentioning that a product has a marketing authorisation

  - adverts relating to products for treatment, prevention or diagnosis of chronic insomnia, diabetes and other metabolic diseases, malignant diseases, serious infectious diseases (including HIV-related diseases), tuberculosis and sexually transmitted diseases

Legislative Changes Advertising Marketing and Promotions

Role of MHRA in Advertising and Promotions

Role of MHRA in Advertising and Promotions

➢ Role of MHRA

- On a daily basis, the Advertising Unit of the MHRA checks:-
  - medical journals
  - magazines
  - the Internet for the promotion of licenses medicines
  - scrutinises advertising prior to issue
  - investigates complaints about advertisements
  - provides advice to industry, health professionals and other regulatory bodies

Role of MHRA in Advertising and Promotions

- **The MHRA's Blue Guide: Advertising and Promotion of Medicines in the UK**
  - In March 2005, MHRA launched its **new guidance on the advertising and promotion of medicines** in the UK called the Blue Guide
  - MHRA's approach is: "**tougher measures against poor practice**", "**greater scrutiny**" and "**greater efficiency**".
  - Supplementary to any legal action the MHRA may take regarding unlawful practices, it will also now publish all its reviews of advertisements on its website as an attempt to name and shame infringing companies

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Role of MHRA in Advertising and Promotions

- **The MHRA's Blue Guide: Advertising and Promotion of Medicines in the UK Cont'd**
  - Companies that regularly breach the Blue Guide subject to review of whole advertising portfolio to ensure meet appropriate standards
  - If potential breach of Advertising Regulations identified, MHRA may request advertiser to amend or withdraw the advertisement, issue a corrective statement, and/or require future advertising for that product to be submitted to the MHRA for review prior to issue ('pre-vetting').
  - Finally, the MHRA has put in place new processes to ensure that advertising is reviewed quickly and meticulously

Codes

Advertising, Marketing and Promotion of Medicines - Codes

➢ Association of the British Pharmaceutical Industry

- The Association of the British Pharmaceutical Industry has its own Code of Practice for the Pharmaceutical Industry, which has been operating for nearly 40 years http://www.abpi.org.uk/publications/pdfs/pmpca_code2006.pdf

- Clause 2 of the Code provides:-
  - that a product cannot be marketed prior to the grant of authorisation which permits its sale or supply;
  - the promotion of the product must not be inconsistent with its authorisation nor be inconsistent with the particulars listed in its summary of product characteristics

- Clause 7 of the Code provides that no information on the product should be **misleading**

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Advertising, Marketing and Promotion of Medicines - Codes

➢ TV Advertising Standards Code

- Section 8 covers advertisements of medicinal products.
- Section 8.2.1 outlines products which cannot be advertised including:
  - medicinal products or treatments available only on prescription
  - products for the treatment of alcohol and substance misuse or dependence (an exception is made for smoking deterrents
  - hypnosis-based procedures, psychiatry, psychology, psychoanalysis and psychotherapy; and
  - services that offer to prescribe or treat remotely

Advertising, Marketing and Promotion of Medicines - Codes

➢ Radio Codes

- Under section 4.4 prescription only medication cannot be advertised

- Section 4.6 states that advertisements for medicinal products must include the following information:
  - the **name of the product** and an **indication of what it is for**;
  - the **name of the active ingredient**, if it contains only one;
  - where necessary, the **information needed for the correct use of the product**; and
  - wording such as ‘always read the label’ or ‘always read the leaflet’, as appropriate

Bioinformatics

Bioinformatics

➢ Definition of Bioinformatics

- Bioinformatics uses computers to store and analyse molecular biological information. This information is used in digital format that can then solve problems of molecular biology, predict structures, and simulate macromolecules. More generally, bioinformatics may be used to describe any use of computers for the purposes of biology, but the molecular-biology specific definition is by far the most common e.g. DNA sequence analysis

- In sequence analysis, DNA sequences of various organisms are stored in databases for easy retrieval and comparison e.g. the well-reported Human Genome Project is an example of sequence analysis bioinformatics

Pharmacovigilence

Pharmacovigilance

- **Definition of Pharmacovigilance**

- Pharmacovigilance the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines

E-Marketing

Legal Implications

➢E-Marketing

- Spams – unsolicited bulk emails
- Spam numbers will double each year - Wall Street, 2003
- Active bulk email addresses – high value and profitable
- Most spam originates from outside the UK
- Compilation and production of email lists – sold to spammers
- Anti-Spam Regulations to stem the flow of spam

  -UK -**Privacy and Electronic Communications (EC Directive) Regulations 2003**

  -US – **CAN-SPAM Act**

Legal Implications

- **Latest Development**
  - Directive
    - **The Privacy and Electronic Communications (2002/58/EC) – see the Privacy and Electronic Communications (EC Directive) Regulations 2003**

      – Constraints on the use of e-mails, SMS marketing and Website cookies

Legal Implications

➢Latest Development

- ❑Regulations – Data Protection, Human Rights and Freedom of Information

  - ❑ **Freedom of Information Act 2000**

  – Requesting information from a public authority (information generally)

  -Come into force January 2005

  -Exemptions for future publications, national security, health and safety

  -Co-ordinated regime with the DPA

Legal Implications

- **Latest Development**
  - Codes of Practice
    - **Information Commissioner Employment Practices Code**
      - Guidance regarding surveillance and monitoring of employees
      - Guidance regarding medical records

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